Hematology Issues during COVID-19

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I. Recommendations
   a. Initial Work up
      i. All patients presenting to MGH for COVID-19 should have the following test obtained at baseline: D-dimer, PT, PTT, fibrinogen and CBC with differential
      ii. In patients who have markedly raised D-dimer (arbitrarily set for now at >2400 ng/mL), admission to hospital should be considered even in the absence of other severity symptoms since this clearly signifies increased thrombin generation (A) [1,2,3,4]
   b. Monitoring
      i. All patients admitted to MGH for COVID-19 should have the following tests obtained at baseline and every 2 days: D-dimer, PT, PTT, fibrinogen and CBC with differential (B) [5] or daily if initial or subsequent D-dimer is elevated.
   c. Management
      i. Patients admitted to MGH for COVID-19 (including non-critically ill) should receive standard prophylactic anticoagulation with LMWH (see Dosing Guidelines) in the absence of any contraindications (active bleeding or platelet count less than 25,000); monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication (C) [1,3,6,9]
         a. If LMWH contraindicated due to renal failure (Creatine Clearance <30mL/min), UFH can be used as an alternative (see Dosing Guidelines).
         b. In obese patients, the recommended dose is 40 mg bid (for renal failure, see Dosing Guidelines)
         c. If history of HIT or HITT, can use fondaparinux.
d. If anticoagulation is contraindicated, patients should have mechanical prophylaxis (e.g., pneumoboots).

ii. An increase in D-dimer is currently NOT an indication to escalate to therapeutic anticoagulation.

iii. In patients who develop worsening coagulopathy and DIC, we advise discussing therapeutic options with heme contact (section II, Dr. Rachel Rosovsky (D) [7,8,9,10]

iv. Patients admitted to MGH who are on anticoagulation at baseline (for atrial fibrillation, h/o VTE, prosthetic valves) and are low risk COVID-19 can remain on their anticoagulant (unless drug interaction with COVID-19 treatments)
   a. If a patient is on a direct oral anticoagulant (DOAC) at time of admission but then requires COVID-19 therapy that interacts with the DOAC, or is/becomes severely ill, that patient should be switched to LMWH (preferred over unfractionated heparin).

v. If patients have confirmed DVT or PE or was on therapeutic anticoagulation prior to hospitalization and now changed to parenteral, the following guidelines are recommended:
   1. LMWH is preferred to avoid frequent blood draws (See Dosing Guidelines for special populations and alternatives for renal failure)
   2. Patients who need to be on Unfractionated Heparin (instead of LMWH) should have their anticoagulation monitored with antiXa levels (as opposed to PTT given that the latter increases in severely ill COVID-19 patients and will then unreliable.

vi. All though DVT and PE have been relative uncommon in COVID-19 infected patients, the elevated D-dimer does present a concern for thromboembolism. It is therefore appropriate to remember that the D-dimer test has improved predictive value when symptoms of thrombosis are present.
   1. Concern for DVT: A swollen leg probably, if possible, should promote a venous doppler study. If DVT is present, patient should be placed on full dose anticoagulation (LMWH preferred, see Dosing Guidelines). If patient unable to get US (eg: due to concern of contamination as our COVID19 numbers increase) and clinical suspicion for DVT is high, we would recommend treating with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing (see Dosing Guidelines).
   2. Concern for PE: The presence of shortness of breath is more challenging. Given the current situation, we would prefer avoiding getting imaging (CTA, ECHO) in all of these patients. Rather, if there is a high clinical suspicion for PE (which would be if a patient has worsening SOB, increase in D-dimer and with imaging findings NOT consistent with worsening COVID-19), we would suggest, if possible, obtaining US and if + DVT, treat with full dose anticoagulation or point of care ECHO and if evidence of right heart strain, treat with full dose anticoagulation. If patient unable to get US or ECHO (eg: due to concern of contamination as our COVID19 numbers increase) and clinical suspicion for DVT or PE is high, we would recommend treating with full dose anticoagulation (unless contraindicated) over obtaining any diagnostics testing (see Dosing Guidelines).
vii. Bleeding is rare in the setting of COVID-19. If bleeding does develop, similar principles to septic coagulopathy as per the ISTH guidelines with respect to blood transfusions may be followed [5]

II. Heme Contact
   a. All coagulation-related COVID-19 issues can be discussed with Dr. Rachel Rosovsky (pager #37021, cell: 617-699-2893)

Notes:
(A) It is already well-established that older individuals and those who have co-morbidities (both groups tend to have higher D-dimer) are more likely to die from COVID-19 infection. [1]
Studies specifically looking at abnormal coagulation parameters have identified markedly elevated D-dimers as one of the predictors of mortality. [2,4]
Huang and colleagues showed that D-dimer levels on admission were higher in patients needing critical care support (median [range] D-dimer level 2400 ng/mL [600–14,400]) than those patients who did not require it (median [range] D-dimer level 0·5 ng/mL [300–800], p=0·0042). [3]
Comments regarding D-dimer: When thrombin is activated, it cleaves fibrinogen into fibrin. The fibrin then polymerizes and is cross-linked by Factor XIII. When such a fibrin clot is generated in any disorder, microvascular or macrovascular, the fibrinolytic system is activated, and plasmin cleaves the cross-linked fibrin into smaller pieces which are the D-dimers. Therefore, the D-dimer reflects the production of cross-linked fibrin and is also affected by hepatic function; D-dimers are cleared by a normal liver but rise with liver dysfunction.

(B) Tang et al noted development of DIC on day 4 in 71.4% of patients who didn’t survive the infection compared to just 1 patient (0.6%) who survived. Researchers also noted a statistically significant increase in D-dimer levels, and PT with a decrease in fibrinogen levels in non-survivors at days 10 and 14. [2,5]

(C) LMWH protects critically ill patients against venous thromboembolism. In addition, LMWH has been shown to have anti-inflammatory properties which may be an added benefit in COVID infection where proinflammatory cytokines are markedly raised. [1,3,6,9]. See dosing instructions below.

(D) Multi-organ failure is more likely in patients with sepsis if they develop coagulopathy and inhibiting thrombin generation may have benefit in reducing mortality. [7,8,9]. As noted in (B), this evidence suggests that monitoring PT, D-dimer, platelet count and fibrinogen can be helpful in determining prognosis in COVID-19 patients and if there is worsening of these parameters, more aggressive critical care support is warranted and consideration should be given for more ‘experimental’ therapies in and blood product support as appropriate [2,5,9]

(E) Subgroup analysis comparing patients by survival noted lower platelet count correlated with mortality. Thrombocytopenia was also associated with over five-fold increased risk of severe COVID-19 illness (OR, 5.1; 95% CI, 1.8-14.6). This suggests thrombocytopenia at presentation may be prognosticator. [10]
Dosing Guidelines (see attached charts) [11]

**Supplemental Table S1:** Chemoprophylaxis Dosing Recommendations

<table>
<thead>
<tr>
<th>Condition</th>
<th>UFH Standard Dose</th>
<th>Enoxaparin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Fondaparinux&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Dabigatran&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Adjustment</td>
<td>5000 units SQ q12h</td>
<td>40 mg SQ q24h</td>
<td>2.5 mg SQ q24h</td>
<td>2.5 mg PC q12h</td>
<td>10 mg PO q24h</td>
<td>110 mg x 1 on post-op day 0 followed by 220 mg q24h</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 40 kg/m²; weight &gt; 120 kg)</td>
<td>120 - 150 kg: 5000 units q8h, &gt; 150 kg: 7500 SQ q8h</td>
<td>CrCl &gt; 30 mL/min: 40 mg SQ q12h</td>
<td>Limited Data, Consult Pharmacy</td>
<td>Limited Data, Consult Pharmacy</td>
<td>Limited Data, Avoid Use</td>
<td>Limited Data, Avoid Use</td>
</tr>
<tr>
<td>Low Body Weight (&lt;50 kg)</td>
<td>5000 units SQ q24h or 2500 units SQ q12h</td>
<td>30 mg SQ q24h</td>
<td>Limited Data, Avoid Use</td>
<td>Limited Data, Avoid Use</td>
<td>Limited Data, Avoid Use</td>
<td>Limited Data, Avoid Use</td>
</tr>
<tr>
<td>Drug-Drug Interactions</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Major DDI Consult Pharmacy</td>
<td>Major DDI Consult Pharmacy</td>
<td>Major DDI Consult Pharmacy</td>
</tr>
</tbody>
</table>

Monitoring: Consult pharmacy or hematology in patients with organ dysfunction, extremes of weight or close monitoring warranted (e.g., high blood risk, failure to thrive); consider drug-specific anti-Xa monitoring.

**Supplemental Table S2:** Therapeutic Parenteral Anticoagulation Recommendations

<table>
<thead>
<tr>
<th>Unfractionated Heparin</th>
<th>Enoxaparin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Fondaparinux&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Thrombolytic&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Dose</td>
<td>500 units/kg bolus + 12 units/kg/hr infusion</td>
<td>1 mg/kg SQ q12h (for normal renal function)</td>
<td>Weight based: &lt; 50 kg: 5 mg SQ q24h; 50-100 kg: 7.5 mg q24h; &gt; 100 kg: 10 mg q24h</td>
<td>0.6 mg/kg/hr</td>
</tr>
<tr>
<td>Renal Adjustment</td>
<td>No Dose Adjustment Necessary</td>
<td>CrCl &gt; 30 mL/min: 1 mg/kg SQ q12h</td>
<td>CrCl &gt; 30 mL/min: Avoid use</td>
<td>See Protocol - Usual Starting Dose: 0.15 mg/kg/hr</td>
</tr>
<tr>
<td>Hepatic Adjustment</td>
<td>No Dose Adjustment Necessary</td>
<td>No Dose Adjustment Necessary</td>
<td>No Dose Adjustment Necessary</td>
<td>Moderate (Child-Pugh B) Hepatic Insufficiency: 0.5 mg/kg/min</td>
</tr>
</tbody>
</table>

Consult pharmacy for renal adjustments.

Abbreviations: AKI – acute kidney injury; BMI – body mass index; DDI – drug-drug interactions; PO – per os (oral route); SQ – subcutaneous route; VTE – venous thromboembolism.

For intermediate LMWH dosing: 1 mg/kg daily (normal renal function); consult pharmacy for renal adjustments.

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References


